REMARKS

Claims 1-8, 14, 15, 19, 32, 33, and 36-55 are pending. Claims 19 and 40-45 have been withdrawn from consideration. By virtue of this response, claims 53 and 54 have been cancelled; claims 1, 5, 15, 37-39, 52, and 55 have been amended; and new claims 56-59 have been added. Accordingly, claims 1-11, 13-18, 32, 33, 36-39 and 46-59 are currently under consideration.

Support for new claims 56 and 57 is found in the specification, such as on page 11, lines 14-17; and page 27, lines 16-36. Support for new claims 58 and 59 is found in the specification, such as on page 21, lines 29-31; page 42, lines 18-30; and page 15, lines 15-17. Accordingly, no new matter is added.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Statement of the Substance of the Interview

Applicant's representative wishes to thank Examiner Gambel for the courtesy of the telephonic interview on October 22, 2008 and October 27, 2008. The rejections raised in the Office Action, and claim amendments that would be helpful in overcoming the rejections in the Office Action were discussed.

Objections

Examiner objects to claim 5 because "non-hodgkins type lymphoma" should be "non-Hodgkin's lymphoma".

Applicant respectfully notes that claim 5 has been amended as suggested by the Examiner. Accordingly, Applicant respectfully requests that this objection be withdrawn.

Claim Rejections – 35 USC § 112

A. Claims 1-8, 14-15, 32-33, 36-39 and 46-55 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification does not contain a written description of the claimed invention in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor (s) had possession of the claimed invention at the time the application was filed. Specifically, the Examiner states that the specification does not provide a sufficient written description for the claimed biological materials of "ATCC Accession No. PTA-110" and "the transfectoma having ATCC deposit number 69119".

Applicant respectfully traverses the rejection. However, in the interest of expediting prosecution, Applicant has amended the claims to delete the recitation of "ATCC Accession No. PTA-110" and "the transfectoma having ATCC deposit number 69119" as suggested by the Examiner.

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

B. Claims 52-54 are rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that there is insufficient written description for genus of S2C6-based anti-CD40 antibodies based upon only three CDRs encompassed by the claimed invention.

Applicant respectfully traverses this rejection. However, in the interest of expediting prosecution, Applicant has amended claim 52 to recite all six CDRs of S2C6 antibody and cancelled claims 53 and 54.

In view of the above, Applicant respectfully requests that the rejection be withdrawn.

Claim Rejections – 35 USC § 103(a)

Claims 1-8, 14-15, 32-33, 36-39 and 46-55 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Siegall et al. (U.S. Patent No. 6,843,989) in view of Li et al. (U.S. Patent No. 6,495,129), Hanna et al. (U.S. 2001/0018041 A1), Grillo-Lopez (U.S. Patent No.6,455,043), and Benoit et al. (Immunopharmacology 35: 129-139, 1996).

Applicant respectfully traverses this rejection, and respectfully submits that the Examiner has not established a *prima facie* case of obviousness.

Claims in the present application recite a method for treating a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal by administering an anti-CD20 antibody, and a CD40 specific binding agent that binds and stimulates CD40, enhances interaction between CD40 and CD40L and arrests the growth of or causes deletion of cells expressing CD40, which CD40 specific binding agent is a chimeric antibody or a humanized antibody derived from S2C6; wherein the CD20 specific binding agent and the CD40 specific binding agent in combination inhibits the neoplastic disease or disorder in the mammal. *See* claim 1. As noted in the previous response, in addition to delivering a stimulatory signal, antibody S2C6 enhances the interaction between CD40 and CD40L. See page 19, lines 29-33. The feature of enhancing the interaction between CD40 and CD40L is different from other anti-CD40 antibodies, such as M2, M3 and G28-5. *See* specification, page 19, lines 20-27; and WO 00/75348, page 54, lines 20-28.

Applicant respectfully submits that the references cited by the Examiner do not provide the teaching, suggestion, or motivation that would have led one of ordinary skill to modify the references or to combine the reference teachings to arrive at the claimed invention.

As noted by the Examiner, Siegall et al. (US 6,843,989) teaches methods of treating cancer with anti-CD40 antibodies including S2C6, but this reference does not teach or suggest the use of an anti-CD40 antibody in combination with an anti-CD20 antibody.

Li et al. does not provide further teaching or motivation to use an anti-CD20 antibody with an anti-CD40 antibody for treating a neoplastic disease or disorder. Li et al. teaches

administration of a human myeloid progenitor inhibitory factor-1 (MPIF-1) with Rituximab or Rituximab with any combination of the components of CHOP. See col. 113, lines 57-61; and col. 147, paragraph 3. Li et al. also teaches administration of a human myeloid progenitor inhibitory factor-1 (MPIF-1) with a cytokine, such as an anti-CD40 agonist or antagonist antibody. See col. 113, lines 63-66; and col. 153, lines 12-18. This reference does not teach or suggest use of an anti-CD20 antibody in combination with an anti-CD40 antibody for treating a neoplastic disorder in a human patient.

Grill-Lopez discloses treating various neoplastic disease or disorder with anti-CD20 antibodies. This reference does not teach or provide the motivation for a combination therapy with an anti-CD20 antibody and an anti-CD40 antibody having the characteristics of antibody S2C6.

Benoit et al. does not provide further motivation to combine a chimeric antibody or a humanized antibody derived from S2C6 with an anti-CD20 antibody in the treatment of a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal. The teachings of Benoit et a. are limited to a single anti-CD40 antibody which is produced by hybridoma G28.5. Data presented in Siegall et al. (US 6,843,989) showed antibody S2C6 enhanced CD40/CD40L interaction in *in vitro* studies. In contrast, under the same experimental conditions the antibody G28-5 either did not enhance or inhibited the interaction between CD40 and CD40L. *See* US 6,843,989, col. 30, line 47 to col. 31, line 34. The claims as amended are directed to an anti-CD40 antibody that binds and stimulates CD40 and enhances interaction between CD40 and CD40L. Benoit et al. does not teach or suggest such as an antibody. Accordingly, one skilled in the art would not view that the teachings in Benoit et al. could be applied to presently claimed invention.

As discussed in the previous response, Hanna et al. do not provide the motivation to use a combination of an anti-CD20 antibody with an antibody having the characteristics of S2C6, *i.e.*, enhancing the interaction between CD40L and CD40. Hanna et al. teaches away from using this combination. Example 3 in Hanna et al. showed that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody Rituxan®. See Table 1. The data in this Example indicates that activation of the CD40L-CD40 pathway by soluble CD40L (sCD40L) generated

resistance of RITUXAN® induced apoptosis in DHL-4 lymphoma cells. In view of the data, one skilled in the art would not be motivated to use an anti-CD40 antibody (such as antibody S2C6) that enhances the interaction between CD40L and CD40 in combination with an anti-CD20 antibody for treating a neoplastic disease or disorder.

In view of the teachings in Siegall, Li et al., Hanna et al., Grillo-Lopez, and Benoit et al., one skilled in the art would not be motivated to administer an anti-CD20 antibody with a chimeric antibody or a humanized antibody derived from antibody S2C6 for treating a neoplastic disease or disorder as claimed.

Although it is known in the art that certain drugs can be used in combination with another drug to enhance the treatment efficacy, it is also well known that it is not predictable which combination of drugs could achieve the enhanced therapeutic effects for a type of cancer in a patient. The references cited by the Examiner do not teach or suggest that the combination therapy with an antibody having characteristics of S2C6 and an anti-CD20 antibody would have an enhanced therapeutic effect in treating neoplastic disease or disorder. Applicant respectfully submits that the references do not provide reasonable expectation of success.

As discussed above and argued in the previous response, data in Hanna et al. indicates that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody, RITUXAN®. In view of this teaching, one skilled in the art would not expect an anti-CD40 antibody that enhances the interaction between CD40 and CD40L in combination with an anti-CD20 antibody would have a better effect in treating B-lymphoma as compared to use of each antibody alone. Benoit et al. only disclose that in an *in vitro* assay, combining antibody G28.5 (an anti-CD40 antibody) with an anti-CD20 antibody resulted in increased inhibition past that produced by the anti-CD40 antibody alone. Siegall et al. showed antibody G28-5 did not enhance and even inhibited the interaction between CD40 and CD40L, in contrast to the antibody S2C6 which enhanced CD40/CD40L interaction in *in vitro* studies. In view of the teachings in these references, one skilled in the art would not reasonably expect that an anti-CD40 antibody having characteristics

of S2C6 in combination with an anti-CD20 antibody would have an enhanced effect in treating a neoplastic disorder or disease.

In addition, as argued in the previous response, the present application shows that the anti-CD20 antibody used in combination with anti-CD40 antibody S2C6 had more than cumulative effect in antitumor activity. Example I of the present application is based on the experiments using anti-CD40 antibody S2C6 and anti-CD20 antibody RITUXAN®. The data in Example I shows that "[s]urvival was extended in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody compared with control animals and animals receiving anti-CD40 antibody or anti-CD20 antibody alone." *See* Specification at page 46, lines 22 -25. This result was not merely a cumulative effect based upon the use of the anti-CD40 antibody and the anti-CD20 antibody. As shown in Figure 4, three out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD40 antibody while five out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD20 antibody. In contrast, ten out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the combination of the anti-CD20 antibody and the anti-CD40 antibody. *See* Figure 4. Further, the "[t]umor volume in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody was significantly reduced compared to control animals and animals receiving anti-C40 antibody or anti-CD20 antibody alone." *See* Specification at page 46, lines 29-33. As shown in Figure 5, one out of ten mice treated with the anti-CD40 antibody alone were tumor free (Ramos lymphoma) while ten out of ten mice treated with the combination of the anti-CD40 antibody and the anti-CD20 antibody were tumor free (Ramos lymphoma). In view of the references cited by the Examiner, this non-cumulative effect shown in Example I was surprising and unexpected.

In view of the above, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness, and claims are not obvious over the references cited by the Examiner. Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn.

Double Patenting

Claims 1-8, 14-15, 32-33, 36-39 and 46-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-18 and 31-53 of co-pending USSN 11/537,559.

Applicant respectfully requests that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/537,559, at which time Applicant will address this issue.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 146392002400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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